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(54) Title: PREVENTION AND TREATMENT OF GASTROINTESTINAL AND BLADDER DISORDERS ASSOCIATED WITH CHEMOTHERAPY OR RADIATION THERAPY USING ACTIVE VITAMIN D COMPOUNDS

(57) Abstract: The present invention relates to a method for preventing, treating, or ameliorating gastrointestinal and bladder disorders in a patient receiving a chemotherapy or radiation therapy comprising administering to the patient a therapeutically effective amount of active vitamin D compound or a mimic thereof. According to the invention, the active vitamin D compound or a mimic thereof may be administered by high dose pulse administration so that high doses of the active vitamin D compound or a mimic thereof can be administered to an animal without inducing severe symptomatic hypercalcemia.



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PREVENTION AND TREATMENT OF GASTROINTESTINAL AND
BLADDER DISORDERS ASSOCIATED WITH CHEMOTHERAPY OR
RADIATION THERAPY USING ACTIVE VITAMIN D COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to a method for preventing, treating or ameliorating gastrointestinal (GI) and bladder disorders induced by or associated with chemotherapy or radiation therapy in an animal by administering to the animal active vitamin D compounds and mimics thereof, preferably by high dose pulse administration.

Related Art

[0002] Cancer therapy often entails the administration of one or more chemotherapeutic agents and/or radiation treatments. The choice of a treatment regimen suitable for a particular patient with a particular cancer depends in part on the cytotoxic agent or radiation treatment and may vary from small doses taken one or more times a day to larger doses taken as infrequently as once a month. Regardless of their mechanism of actions, cytotoxic agents and radiation either kill cancer cells outright or slow down or stop cancer cell division. The success of the treatment depends on its differential effect on cancer cells compared to normal cells, i.e., its therapeutic index.

[0003] In addition to treating or ameliorating cancer, chemotherapeutic agents and radiation therapy usually cause unwanted side effects. Some of these side effects may be mild and treatable (such as dizziness, nausea, and some vomiting and/or diarrhea) while others are severe or life-threatening. Among the more serious side effects are GI-related symptoms, including severe vomiting or diarrhea, GI bleeding, stomatitis, mucositis, dehydration, malabsorption, and loss of body weight. These symptoms often limit the dose

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or frequency of chemotherapeutic agent or radiation treatment that a patient can tolerate, thereby compromising treatment of the cancer.

[0004] There are few approved compounds which provide direct protection from injuries caused by chemotherapy. One agent that has been reported to protect the kidney from injury caused by bolus infusions of cisplatin is S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR 2721). (See Glover, D. *et al.*, *Pharmacol. Therap.* 39: 3-7(1988)). However, administered doses caused hypotension (7% of patients) and emesis (48% of patients). Other protective agents include granulocyte-colony stimulating factor, granulocyte/macrophage-colony stimulating factor, E-type prostaglandins (U.S. Patent No. 5,605,931), d-methionine (U.S. Patent No. 6,187,817), 5-chloro-6-(2-iminopyrrolidin-1-yl)methyl-2,4(1H,3H)-pyrimidinedione (U.S. Patent No. 6,479,500), camptothecin derivatives (U.S. Patent No. 6,476,043), caspase inhibitors (U.S. Patent No. 6,566,338), and NF- κ B inhibitors (U.S. Patent No. 6,841,578).

[0005] It is desirable to provide effective protection against GI toxicities induced by or associated with chemotherapy and radiation therapy both to allow for "full dose on time" chemotherapy and to prevent toxicity side effects and complications of the therapy itself. It would be desirable that such protection is provided by a simple procedure which would assure compliance and not interfere with the beneficial therapeutic effects of the chemotherapy agents or radiation treatments. The present invention provides for such a protection.

SUMMARY OF THE INVENTION

[0006] One aspect of the present invention is a method for preventing, treating or ameliorating GI and bladder disorders in a patient receiving chemotherapy and/or radiation therapy comprising administering to said patient a therapeutically effective amount of an active vitamin D compound or a mimic thereof.

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[0007] In one embodiment of the invention, the active vitamin D compound is administered intermittently at a dose sufficient to reduce the adverse effects of chemotherapy and/or radiation therapy on the gastrointestinal and bladder tissues while not diminishing the therapeutic activities on the cancer, thereby expanding the therapeutic index for the therapy program and limiting the patient's need to tolerate the effects of the therapy on the gastrointestinal and bladder tissues. In an additional embodiment, the active vitamin D compound or mimic thereof is administered by high dose pulse administration (HDPA) so that high doses of the active vitamin D compound or mimic thereof can be administered to an animal without inducing severe symptomatic hypercalcemia. In another embodiment of the invention, the active vitamin D compound is administered at a dose sufficient to obtain a peak plasma concentration of the active vitamin D compound that is therapeutically effective.

[0008] In another embodiment, the active vitamin D compound is administered as a unit dosage form comprising about 10 µg to about 75 µg of calcitriol, more preferably about 45 µg. In another embodiment, the active vitamin D compound is administered as part of a formulation comprising about 50% MIGLYOL 812 and about 50% tocopherol PEG-1000 succinate (vitamin E TPGS). The active vitamin D compound may be administered orally, intravenously, parenterally, rectally, topically, nasally or transdermally.

[0009] In a further embodiment, the active vitamin D compound is administered with one or more other therapeutic agents useful for preventing, treating or ameliorating GI disorders in a patient.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The present invention provides a method for protecting GI and bladder cells and tissues from injury produced by chemotherapeutic agents or radiation therapy. Specifically, it has been surprisingly discovered that late stage prostate cancer patients (i.e., patients with androgen independent prostate cancer) treated with Taxotere® and intermittent high doses of calcitriol (e.g.,

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doses as high as 300 µg/day) experienced fewer GI disorders, including nausea, vomiting, diarrhea, and dehydration. Prevention or treatment of these side effects is beneficial in reducing the morbidity of cancer chemotherapy and radiation therapy and/or, allowing for a higher and more curative dose regimen of chemotherapy or radiation therapy to be delivered to cancer patients without these severe side effects.

[0011] Accordingly, the present invention relates to a method for preventing, treating, or ameliorating side effects induced by or associated with chemotherapy or radiation therapy. In particular, the method relates to prevention, treatment, or amelioration of GI and bladder disorders induced by or associated with the chemotherapy or radiation therapy of a variety of cancers including, but not limited to, brain cancer, breast cancer, gastrointestinal cancers comprising colon, colorectal, esophageal, gastric, hepatocellular, pancreatic and rectal cancers, genitourinary cancers comprising bladder, prostate, renal cell and testicular cancers, gynecologic cancers comprising cervical, endometrial, ovarian and uterine cancers, head and neck cancer, leukemias comprising acute lymphoblastic, acute myelogenous, acute promyelocytic, chronic lymphocytic, chronic myelogenous, and hairy cell leukemias, non-small-cell and small-cell lung cancers, Hodgkin's and non-Hodgkin's lymphomas, melanoma, multiple myeloma, and sarcoma.

[0012] In one aspect of the invention, the active vitamin D compound has a reduced hypercalcemic effect, allowing higher doses of the compound to be administered to an animal without inducing severe symptomatic hypercalcemia. The reduced hypercalcemic effect may be due to the active vitamin D compound itself, the regimen by which the compound is administered, or both.

[0013] The term "GI and bladder disorders induced by or associated with," as used herein, refers to any GI and/or bladder disorder that a patient may develop during or after chemotherapy or radiation therapy. This term is intended to include all GI and bladder disorders a patient may suffer during or after chemotherapy or radiation therapy, regardless of whether a direct or indirect causal link between the therapy and the disorder can be demonstrated.

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GI and bladder disorders include acute disorders occurring within 48 hours of the onset of therapy and delayed disorders occurring several days to several weeks after therapy has ended. In one embodiment, GI and bladder disorders that develop within eight weeks after the end of chemotherapy or radiation therapy are included in "GI and bladder disorders induced by or associated with" chemotherapy or radiation therapy.

[0014] The term, "GI disorder," as used herein, refers to any disorder associated with any part of the GI tract, including the mouth, esophagus, stomach, small intestine, large intestine, and rectum. GI disorders include, but are not limited to, nausea, vomiting, diarrhea, GI bleeding, esophagitis, stomatitis, xerostomia, mucositis, pancreatitis, colitis, proctitis, fibrosis, constipation, abdominal cramps, abdominal pain, dehydration, malabsorption, anorexia, and weight loss.

[0015] The term, "bladder disorder," as used herein, refers to any disorder associated with the bladder. Bladder disorders include, but are not limited to, mucositis, cystitis, hemorrhagic cystitis, dysuria, urinary retention, hematuria, and bladder pain.

[0016] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in prevention of a chemotherapy and/or radiation therapy induced or associated GI or bladder disorder, *e.g.*, nausea, vomiting, diarrhea, GI bleeding, stomatitis, mucositis, dehydration, malabsorption, weight loss, cystitis, hemorrhagic cystitis, dysuria, urinary retention, hematuria, or bladder pain, amelioration of one or more symptoms of a GI or bladder disorder, or prevention of advancement of a GI or bladder disorder. For example, a therapeutically effective amount preferably refers to the amount of a therapeutic agent that reduces the extent of GI or bladder symptoms by at least 10%, preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100%. The extent of GI and bladder disorders can be determined by any method known in the art.

[0017] The terms "prevent, preventing, and prevention," as used herein, are intended to refer to a decrease in the occurrence of a chemotherapy and/or

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radiation therapy induced or associated GI or bladder disorder. The prevention may be complete, *e.g.*, the total absence of a GI or bladder disorder. The prevention may also be partial, such that GI or bladder disorder is less than that which would have occurred without the present invention. For example, the extent of GI or bladder disorder using the methods of the present invention may be at least 10%, preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% less than the amount of GI or bladder disorder that would have occurred without the present invention.

[0018] Chemotherapeutic agents useful in the invention include any agent that has been used, is currently used, is known to be useful, or is identified in the future to be useful for the treatment of cancer, and include both chemical and biological agents. Examples of chemotherapeutic agents include, but are not limited to, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacytidine, BCG live, bevaceizumab, bexarotene, bleomycin, bortezomib, busulfan, calusterone, camptothecin, capecitabine, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cinacalcet, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone, Elliott's B solution, epirubicin, epoetin alfa, estramustine, etoposide, exemestane, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gemcitabine, gentuzumab, ozogamicin, gefitinib, goserelin, hydroxyurea, ibritumomab, tiuxetan, idarubicin, ifosfamide, imatinib, interferon alfa-2a, interferon alfa-2b, irinotecan, letrozole, leucovorin, levamisole, lomustine, meclorethamine, megestrol, melphalan, mercaptopurine, mesna, methotrexate, methoxsalen, methylprednisolone, mitomycin C, mitotane, mitoxantrone, nandrolone, nofetumomab, oblimersen, oprelvekin, oxaliplatin, paclitaxel, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed, pentostatin, pipobroman, plicamycin, polifeprosan, porfimer, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, SN-38, streptozocin, talc, tamoxifen, tarceva, temozolomide, teniposide,

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testolactone, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, and zoledronate.

[0019] Chemotherapeutic agents also include anti-inflammatory drugs which are known to be useful for ameliorating inflammation. Suitable anti-inflammatory drugs include, but are not limited to, salicylates (such as aspirin, choline magnesium trisalicylate, methyl salicylate, salsalte and diflunisal), acetic acids (such as indomethacin, sulindac, tolmetin, aceclofenac and diclofenac), 2 arylpropionic acids or profens (such as ibuprofen, ketoprofen, naproxen, fenoprofen, flurbiprofen and oxaprozin), N-arylanthranilic acids or fenamic acids (such as mefenamic acid, flufenamic acid, and meclofenamate), enolic acids or oxicams (such as piroxicam and meloxicam), cox inhibitors (such as celecoxib, rofecoxib (withdrawn from market), valdecoxib, parecoxib and etoricoxib), sulphonanilides such as nimesulide; naphthylalkanones (such as nabumetone), pyranocarboxylic acids (such as etodolac) and pyrroles (such as ketorolac).

[0020] Chemotherapeutic agents further include immunomodulatory agents. As used herein, the term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, immunomodulants, immunomodulators or immunomodulatory drugs, refer to an agent that modulates a host's immune system. In particular, an immunomodulatory agent is an agent that alters the ability of a subject's immune system to respond to one or more foreign antigens. In a specific embodiment, an immunomodulatory agent is an agent that shifts one aspect of a subject's immune response, e.g., the agent shifts the immune response from a Th1 to a Th2 response. In certain embodiments, an immunomodulatory agent is an agent that inhibits or reduces a subject's immune system (i.e., an immunosuppressant agent). In certain other embodiments, an immunomodulatory agent is an agent that activates or increases a subject's immune system (i.e., an immunostimulatory agent).

[0021] Immunomodulatory agents useful for the present invention include, but are not limited to, small molecules, peptides, polypeptides, proteins, nucleic

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acids (e.g., DNA and RNA nucleotides including, but not limited to, antisense nucleotide sequences, triple helices and nucleotide sequences encoding biologically active proteins, polypeptides or peptides), antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules. A particularly useful immunomodulatory agent for the treatment of cancer is thalidomide.

[0022] Examples of immunosuppressant agents useful for the treatment of cancer include glucocorticoid receptor agonists (e.g., cortisone, dexamethasone, hydrocortisone, betamethasone), calcineurin inhibitors (e.g., macrolides such as tacrolimus and pimecrolimus), immunophilins (e.g., cyclosporin A) and mTOR inhibitors (e.g., sirolimus, marketed as RAPAMUNE® by Wyeth). Immunostimulant agents useful for the treatment of cancer include interferon and Zidovudine (AZT).

[0023] Radiation therapy useful in the invention includes any therapy that has been used, is currently used, or is known to be useful for the treatment of cancer. Examples of radiation therapy include, but are not limited to, brachytherapy, radionuclide therapy, external-beam radiation therapy, thermotherapy (cryoablation therapy, hyperthermic therapy), radiosurgery, charged-particle radiotherapy, neutron radiotherapy, and photodynamic therapy.

[0024] Therapeutic agents useful as adjunctive therapy according to the invention include, but are not limited to, small molecules, synthetic drugs, peptides, polypeptides, proteins, nucleic acids (e.g., DNA and RNA polynucleotides including, but not limited to, antisense nucleotide sequences, triple helices, and nucleotide sequences encoding biologically active proteins, polypeptides, or peptides), antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules. Any agent which is known to be useful, or which has been used or is currently being used for the prevention, treatment, or amelioration of GI or bladder disorders can be used in combination with an active vitamin D compound in accordance with the invention described herein. In one embodiment,

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therapeutic agents may be anti-inflammatory agents, antibiotics, anti-emetic agents, anti-apoptotic agents, anti-anorexic agents, or anti-GI bleeding agents.

[0025] Anti-inflammatory agents suitable for preventing, treating, or ameliorating GI or bladder disorders include, but are not limited to, salicylates such as aspirin, methyl salicylate and diflunisal; arylalkanoic acids such as indomethacin, sulindac and diclofenac; 2-arylpropionic acids (profens) such as ibuprofen, ketoprofen, naproxen and ketorolac; N-arylanthranilic acids (fenamic acids) such as mefenamic acid; oxicams such as piroxicam and meloxicam; cox inhibitors such as celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib; and sulphonanilides such as nimesulide.

[0026] Antibiotics useful for preventing, treating, or ameliorating GI or bladder disorders include, but are not limited to, aminoglycosides, beta-lactams, glycopeptide antibiotics, macrolides, oxazolidinones, polymyxins, quinolones (fluoroquinolones), streptogramins, sulfonamides and tetracyclines. Aminoglycosides include amikacin, dibekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, streptomycin and tobramycin. Beta-lactams include carbapenems such as ertapenem, imipenem and meropenem; cephalosporins such as cephalexin, cefuroxime, cefadroxil and penicillins. Penicillins include benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, dicloxacillin, flucloxacillin, amoxicillin, ampicillin, piperacillin, ticarcillin, azlocillin and carbenicillin. Glycopeptide antibiotics include vancomycin, teicoplanin, ramoplanin and decaplanin. Macrolides suitable as antibiotics include erythromycin, azithromycin, clarithromycin, roxithromycin and ketolides. Oxazolidinones suitable as antibiotics include linezolid and quinupristin/dalfopristin. Polymyxins suitable as an antibiotic include polymyxin B and colistin. Quinolones (fluoroquinolones) suitable as an antibiotic include ciprofloxacin, enoxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, sparfloxacin, ofloxacin, trovafloxacin and nalidixic acid. Tetracyclines suitable as an antibiotic include doxycycline, oxytetracycline and chlortetracycline.

- [0027] Anti-emetic agents suitable for preventing, treating, or ameliorating GI disorders include, but are not limited to, serotonin antagonists (*e.g.*, metoclopramide, ondansetron, granisetron, propisetron, dolasetron), corticosteroids (*e.g.*, dexamethasone), dopamine antagonists (*e.g.*, prochlorperazine, chlorpromazine, thiethylperazine, haloperidol), and cannabinoids (*e.g.*, dronabinol).
- [0028] Anti-apoptotic agents suitable for preventing, treating, or ameliorating GI or bladder disorders include, but are not limited to, caspase inhibitors (*e.g.*, compounds disclosed in U.S. Patent No. 6,566,338, incorporated herein in its entirety) and anti-apoptotic Bcl-2 family member inhibitors (*e.g.*, gossypol).
- [0029] Anti-anorexic agents suitable for preventing, treating, or ameliorating GI disorders include, but are not limited to, megestrol acetate, corticosteroids (*e.g.*, dexamethasone, prednisolone, methylprednisolone), metoclopramide, anabolic steroids (*e.g.*, nandrolone decanoate), hydrazine sulfate, cyproheptadine, indomethacin, pentoxifylline, and cannabinoids (*e.g.*, dronabinol).
- [0030] Anti-GI bleeding agents suitable for preventing, treating, or ameliorating GI disorders include, but are not limited to, antacids, H₂-receptor antagonists (*e.g.*, cimetidine, ranitidine, famotidine), and sucralfate.
- [0031] The term “an active vitamin D compound in combination with one or more therapeutic agents,” as used herein, is intended to refer to the combined administration of an active vitamin D compound and one or more therapeutic agents, wherein the active vitamin D compound can be administered prior to, concurrently with, or after the administration of the therapeutic agents. The active vitamin D compound can be administered up to three months prior to or after the therapeutic agents and still be considered to be a combination treatment.
- [0032] The term “active vitamin D compound,” as used herein, is intended to refer to a vitamin D compound that is or becomes biologically active (*e.g.*, binds to and stimulates the vitamin D receptor) when administered to a subject or contacted with cells. Active vitamin D compounds include compounds that cause hypercalcemia and compounds that do not cause hypercalcemia upon

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administration. The biological activity of a vitamin D compound can be assessed by assays well known to one of skill in the art, *e.g.*, immunoassays that measure the expression of a specific gene regulated by vitamin D. Vitamin D compounds exist in several forms with different levels of activity in the body. For example, a vitamin D compound may be partially activated by first undergoing hydroxylation in the liver at the carbon-25 position and then may be fully activated in the kidney by further hydroxylation at the carbon-1 position. The prototypical active vitamin D compound is 1 α ,25-hydroxyvitamin D₃, also known as calcitriol. A large number of other active vitamin D compounds are known and can be used in the practice of the invention. The active vitamin D compounds of the present invention include, but are not limited to, analogs, homologs, mimics, and derivatives of vitamin D compounds such as those described in the following patents: U.S. Patent Nos. 4,391,802 (1 α -hydroxyvitamin D derivatives); 4,717,721 (1 α -hydroxy derivatives with a 17 side chain greater in length than the cholesterol or ergosterol side chains); 4,851,401 (cyclopentano-vitamin D analogs); 4,866,048 and 5,145,846 (vitamin D₃ analogues with alkynyl, alkenyl, and alkanyl side chains); 5,120,722 (trihydroxycalciferol); 5,547,947 (fluoro-cholecalciferol compounds); 5,446,035 (methyl substituted vitamin D); 5,411,949 (23-oxa-derivatives); 5,237,110 (19-nor-vitamin D compounds); 4,857,518 (hydroxylated 24-homo-vitamin D derivatives). Particular examples include ROCALTROL (Roche Laboratories); CALCIJEX injectable calcitriol; investigational drugs from Leo Pharmaceuticals including EB 1089 (24a,26a,27a-trihomo-22,24-diene-1 α ,25-(OH)₂-D₃, KH 1060 (20-epi-22-oxa-24a,26a,27a-trihomo-1 α ,25-(OH)₂-D₃), MC 1288 (1,25-(OH)₂-20-epi-D₃) and MC 903 (calcipotriol, 1 α 24s-(OH)₂-22-ene-26,27-dehydro-D₃); Roche Pharmaceutical drugs that include 1,25-(OH)₂-16-ene-D₃, 1,25-(OH)₂-16-ene-23-yne-D₃, and 25-(OH)₂-16-ene-23-yne-D₃; Chugai Pharmaceuticals 22-oxacalcitriol (22-oxa-1 α ,25-(OH)₂-D₃; 1 α -(OH)-D₅ from the University of Illinois; and drugs from the Institute of Medical Chemistry-Schering AG that include ZK 161422 (20-methyl-1,25-(OH)₂-D₃) and ZK 157202 (20-methyl-23-ene-1,25-(OH)₂-D₃); 1 α -(OH)-D₂; 1 α -(OH)-D₃, 1 α -(OH)-D₄, 25-(OH)-D₂;

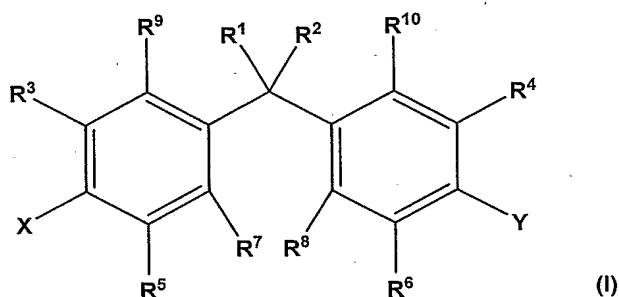
25-(OH)-D₃; and 25-(OH)-D₄. Additional examples include 1 α ,25-(OH)₂-26,27-d₆-D₃; 1 α ,25-(OH)₂-22-ene-D₃; 1 α ,25-(OH)₂-D₃; 1 α ,25-(OH)₂-D₂; 1 α ,25-(OH)₂-D₄; 1 α ,24,25-(OH)₃-D₃; 1 α ,24,25-(OH)₃-D₂; 1 α ,24,25-(OH)₃-D₄; 1 α -(OH)-25-FD₃; 1 α -(OH)-25-FD₄; 1 α -(OH)-25-FD₂; 1 α ,24-(OH)₂-D₄; 1 α ,24-(OH)₂-D₃; 1 α ,24-(OH)₂-D₂; 1 α ,24-(OH)₂-25-FD₄; 1 α ,24-(OH)₂-25-FD₃; 1 α ,24-(OH)₂-25-FD₂; 1 α ,25-(OH)₂-26,27-F₆-22-ene-D₃; 1 α ,25-(OH)₂-26,27-F₆-D₃; 1 α ,25S-(OH)₂-26-F₃-D₃; 1 α ,25-(OH)₂-24-F₂-D₃; 1 α ,25S,26-(OH)₂-22-ene-D₃; 1 α ,25R,26-(OH)₂-22-ene-D₃; 1 α ,25-(OH)₂-D₂; 1 α ,25-(OH)₂-24-epi-D₃; 1 α ,25-(OH)₂-23-yne-D₃; 1 α ,25-(OH)₂-24R-F-D₃; 1 α ,25S,26-(OH)₂-D₃; 1 α ,24R-(OH)₂-25F-D₃; 1 α ,25-(OH)₂-26,27-F₆-23-yne-D₃; 1 α ,25R-(OH)₂-26-F₃-D₃; 1 α ,25,28-(OH)₃-D₂; 1 α ,25-(OH)₂-16-ene-23-yne-D₃; 1 α ,24R,25-(OH)₃-D₃; 1 α ,25-(OH)₂-26,27-F₆-23-ene-D₃; 1 α ,25R-(OH)₂-22-ene-26-F₃-D₃; 1 α ,25S-(OH)₂-22-ene-26-F₃-D₃; 1 α ,25R-(OH)₂-D₃-26,26,26-d₃; 1 α ,25S-(OH)₂-D₃-26,26,26-d₃; and 1 α ,25R-(OH)₂-22-ene-D₃-26,26,26-d₃. Additional examples can be found in U.S. Patent No. 6,521,608. *See also, e.g.*, U.S. Patent Nos. 6,503,893, 6,482,812, 6,441,207, 6,410,523, 6,399,797, 6,392,071, 6,376,480, 6,372,926, 6,372,731, 6,359,152, 6,329,357, 6,326,503, 6,310,226, 6,288,249, 6,281,249, 6,277,837, 6,218,430, 6,207,656, 6,197,982, 6,127,559, 6,103,709, 6,080,878, 6,075,015, 6,072,062, 6,043,385, 6,017,908, 6,017,907, 6,013,814, 5,994,332, 5,976,784, 5,972,917, 5,945,410, 5,939,406, 5,936,105, 5,932,565, 5,929,056, 5,919,986, 5,905,074, 5,883,271, 5,880,113, 5,877,168, 5,872,140, 5,847,173, 5,843,927, 5,840,938, 5,830,885, 5,824,811, 5,811,562, 5,786,347, 5,767,111, 5,756,733, 5,716,945, 5,710,142, 5,700,791, 5,665,716, 5,663,157, 5,637,742, 5,612,325, 5,589,471, 5,585,368, 5,583,125, 5,565,589, 5,565,442, 5,554,599, 5,545,633, 5,532,228, 5,508,392, 5,508,274, 5,478,955, 5,457,217, 5,447,924, 5,446,034, 5,414,098, 5,403,940, 5,384,313, 5,374,629, 5,373,004, 5,371,249, 5,430,196, 5,260,290, 5,393,749, 5,395,830, 5,250,523, 5,247,104, 5,397,775, 5,194,431, 5,281,731, 5,254,538, 5,232,836, 5,185,150, 5,321,018, 5,086,191, 5,036,061, 5,030,772, 5,246,925, 4,973,584, 5,354,744, 4,927,815, 4,804,502, 4,857,518, 4,851,401, 4,851,400, 4,847,012, 4,755,329, 4,940,700, 4,619,920, 4,594,192, 4,588,716, 4,564,474, 4,552,698, 4,588,528, 4,719,204, 4,719,205, 4,689,180, 4,505,906, 4,769,181, 4,502,991, 4,481,198, 4,448,726,

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4,448,721, 4,428,946, 4,411,833, 4,367,177, 4,336,193, 4,360,472, 4,360,471, 4,307,231, 4,307,025, 4,358,406, 4,305,880, 4,279,826, and 4,248,791.

[0033] The term "mimic" as used herein is intended to refer to non-secosteroidal vitamin D mimic compounds. In general, these non-secosteroidal vitamin D mimics are compounds that do not structurally fall within the class of compounds generally known as vitamin D compounds but which modulate the activity of vitamin D nuclear receptors. Examples of such vitamin D mimics include bis-aryl derivatives disclosed by U.S. Patent 6,218,430 and WO publication 2005/037755. Additional examples of non-secosteroidal vitamin D mimic compounds suitable for the present invention can be found in U.S. patents 6,831,106; 6,706,725; 6,689,922; 6,548,715; 6,288,249; 6,184,422, 6,017,907, 6,858,595 and 6,358,939.

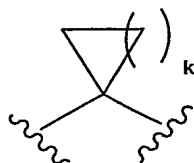
[0034] In one aspect the invention is drawn to methods employing non-secosteroidal vitamin D mimic compounds having Formula I:



wherein:

R^1 and R^2 are each independently halo, haloalkyl, pseudohalo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl; or

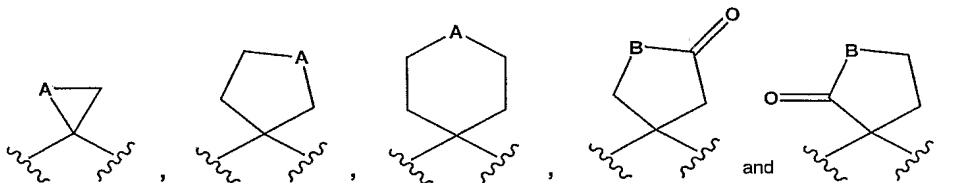
R^1 and R^2 , together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl consisting of:



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wherein k is an integer from 1 to 6; or

R^1 and R^2 , together with the carbon atom to which they are attached, form an optionally substituted heterocyclyl selected from a group consisting of:



wherein A is -O-, -NR^x-, -S-, -S(O)- or -S(O)₂- wherein R^x is hydrogen, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -R¹⁴-C(J)R¹⁵, -R¹⁴-C(J)OR¹⁵, -R¹⁴-C(J)R¹⁶OR¹⁵, -R¹⁴-C(J)SR¹⁶, -R¹⁴-C(J)N(R¹⁸)R¹⁹, -R¹⁴-C(J)N(R¹⁷)N(R¹⁸)R¹⁹, -R¹⁴-C(J)N(R¹⁷)S(O)_pR²⁰, -R¹⁴-S(O)_pN(R¹⁸)R¹⁹, or -R¹⁴-S(O)_pR²⁰; and wherein B is -O-, -S- or -NR^y where R^y is hydrogen, alkyl, haloalkyl, aryl or heteroaryl; and wherein each p is independently 0 to 2;

R^3 and R^4 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, pseudohalo, nitro, cyano, azido, -R¹⁴-OR¹⁵, -R¹⁴-N(R¹⁸)R¹⁹, -R¹⁴-SR¹⁵, -R¹⁴-OC(J)R¹⁵, -R¹⁴-NR¹⁷C(J)R¹⁵, -R¹⁴-OC(J)N(R¹⁸)R¹⁹, -R¹⁴-NR¹⁷C(J)N(R¹⁸)R¹⁹, -R¹⁴-NR¹⁷C(J)OR¹⁵, -R¹⁴-C(J)R¹⁵, -R¹⁴-C(J)OR¹⁵, -R¹⁴-C(J)SR¹⁵, -R¹⁴-C(J)N(R¹⁸)R¹⁹, or -R¹⁴-C(J)N(R¹⁷)N(R¹⁸)R¹⁹;

$R^5, R^6, R^7, R^8, R^9, R^{10}$ are each independently hydrogen, halo, hydroxy, amino, pseudohalo, cyano, nitro, alkyl, haloalkyl, alkoxy or haloalkoxy;

X is R²⁵;

Y is independently R³⁰, -OR³¹, -SR³² or -N(R³³)(R³⁴);

R²⁵ and R³⁰ are each independently selected from (i) or (ii) as follows:

(i) optionally substituted alkyl that may be substituted with one to ten substituents each independently selected from a group consisting of halo, pseudohalo, nitro, cyano, thioxo, azido, amidino, guanidino, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally

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substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$, $-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$ and $-C(=NR^{17})N(R^{18})R^{19}$; or

(ii) optionally substituted alkenyl or optionally substituted alkynyl, either of which may be substituted with one to ten substituents each independently selected from a group consisting of oxo, thioxo, halo, pseudohalo, nitro, cyano, azido, amidino, guanidino, $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-S(O)_pR^{20}$, $-N(R^{17})S(O)_pR^{20}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$, $-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})S(O)_pR^{20}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$, $-C(=NR^{17})N(R^{18})R^{19}$, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{31} , R^{32} , R^{33} , and R^{34} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl or optionally substituted cycloalkyl; all of which may be optionally substituted with one to ten substituents each independently selected from a group consisting of oxo, halo, pseudohalo, nitro cyano, azido, amidino, guanidino $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-S(O)_pR^{20}$, $-N(R^{17})S(O)_pR^{20}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$, $-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})S(O)_pR^{20}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$, $-C(=NR^{17})N(R^{18})R^{19}$, alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, and R^{34} can additionally be hydrogen;

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where each R^{14} is independently a direct bond or alkylene;

where each R^{15} and R^{17} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, cyano, hydroxy and amino;

where each R^{16} and R^{20} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, hydroxy, alkoxy and amino; and

where each R^{18} and R^{19} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, hydroxy, alkoxy and amino;

or where R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl;

each R^{21} is independently alkyl, $-OR^{22}$ or $-N(R^{23})R^{24}$;

R^{22} is hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or aralkyl;

R^{23} and R^{24} are each independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl or cycloalkyl;

or R^{23} and R^{24} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl;

each J is independently O or S;

as a single isomer, a mixture of isomers, or as a racemic mixture of isomers; as a solvate or polymorph; or as a prodrug or metabolite; or as a pharmaceutically acceptable salt thereof.

[0035] In one embodiment, R¹ and R² may form a substituted cyclohexyl, said cyclohexyl, when substituted at the 4-position relative to the gem-diaryl substituents, may be substituted with a substituent selected from the group consisting of halo, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0036] In another embodiment, R²⁵ and R³⁰ are not -CH₂COOH; -CH₂-5-tetrazolyl; -CH₂COOMe; -CH₂COOEt; -CH₂NH(CH₂COOH); -CH₂N(C(O)Me)(CH₂COOH); -CH₂-N-pyrrolidin-2-one; -CH₂-(1-methylpyrrolidin-2-one-3-yl); -CH₂C(O)NH₂; -CH₂C(O)NMe₂; -CH₂C(O)NHMe; -CH₂C(O)-N-pyrrolidone; -CH(OH)COOH; -CH(OH)C(O)NH₂; -CH(OH)C(O)NHMe; -CH(OH)C(O)NMe₂; -CH(OH)C(O)NEt₂; -CH₂CH₂COOH; -CH₂CH₂COOMe; -CH₂CH₂COOEt; -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NHMe; -CH₂CH₂C(O)NMe₂; or -CH₂CH₂-5-tetrazolyl.

[0037] In another aspect the invention is drawn to methods employing the following non-secosteroidal vitamin D mimic compounds:

3-(2-methyl-4-{2,2,2-trifluoro-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-1-phenyl-ethyl}-phenoxy)-propane-1,2-diol;

3-(4-{4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-propane-1,2-diol;

3-(4-{4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

1-{4-[4-(2(S),3-dihydroxy-propoxy)-3-methyl-phenyl]-4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-1-yl}-ethanone;

1-(4-{1-acetyl-4-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one;

3-(4-{1-ethyl-1-[4-(3-hydroxy-3-methylbutyl)-3-methylphenyl]-propyl}-2-methylphenoxy)-propane-1,2(S)-diol;

3-(4-{1-ethyl-1-[4-(3-ethyl-3-hydroxypentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

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3-(4-{1-ethyl-1-[4-(3-hydroxy-5-methylhexyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-(4-{1-ethyl-1-[4-(3-hydroxy-4-methylpentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-(2-ethyl-4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-3-methylphenyl]-propyl}-phenoxy)-propane-1,2(S)-diol;

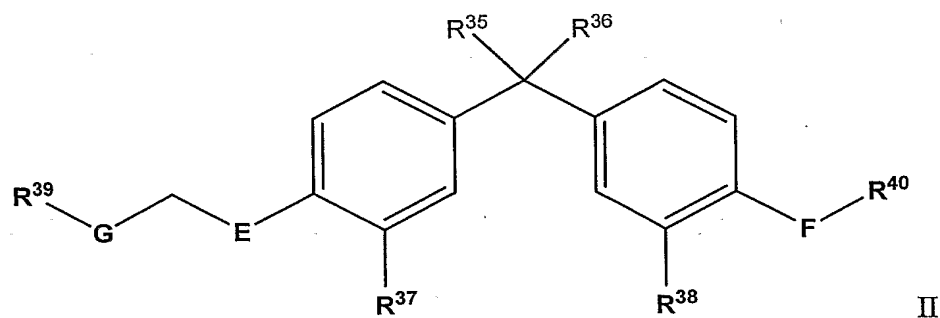
3-(4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-[4-(1-ethyl-1-{4-[3(S)-hydroxy-4,4-dimethylpentyl]-3-methylphenyl}-propyl)-2-methyl-phenoxy]-propane-1,2(S)-diol;

3-[4-(1-ethyl-1-{4-[3(R)-hydroxy-4,4-dimethylpentyl]-3-methylphenyl}-propyl)-2-methyl-phenoxy]-propane-1,2(S)-diol and

3-(4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-phenyl]-propyl}-2-methylphenoxy)-propane-1,2(S)-diol.

[0038] In another aspect the invention is drawn to methods employing non-secosteroidal vitamin D mimic compounds having Formula II:



wherein:

E and F are each independently selected from the group consisting of O, S, and NR⁴¹;

G is selected from the group consisting of C=O, CH(OR⁴²), and CH(NR⁴³ R⁴⁴);

R³⁵ and R³⁶ are independently selected from the group consisting of alkyl groups, optionally fluorinated; or together R³⁵ and R³⁶ form a cycloalkylidene having 3 to 8 carbon atoms, optionally fluorinated;

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R^{37} and R^{38} are independently selected from the group consisting of halogen; lower n-alkyl, optionally fluorinated; and lower alkoxy, optionally fluorinated;

R^{39} is selected from the group consisting of H; optionally substituted alkyl groups; optionally substituted alkenyl groups; optionally substituted alkynyl groups; optionally substituted aryl groups; OR^{45} ; $NR^{46}R^{47}$; or together with R^{42} , R^{43} , or R^{44} forms a 3- to 12-membered cyclic group wherein said cyclic group is selected from the group consisting of amidines, amines, ethers, lactams, lactones, ketals, hemiketals, amins, hemiaminals, carbonates, carbamates, ureas, and combinations thereof;

R^{40} is selected from the group consisting of H and alkyl groups, optionally substituted;

R^{41} is selected from the group consisting of H and alkyl groups, optionally substituted;

R^{42} is selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl group, and optionally substituted acyl groups;

R^{43} and R^{44} are independently selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups;

R^{45} is selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups; and

R^{46} and R^{47} are independently selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups and pharmaceutically acceptable salts thereof.

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[0039] In a first embodiment, when K and L are both O, M is C=O, and R⁴⁵ is selected from the group consisting of OH and C₁-C₄ alkoxy, then R⁴⁶ is not carboxymethyl and alkyl esters thereof. In a second embodiment, when K and L are both O, and M is selected from the group consisting of CH(OR⁴⁸) and CH(NR⁴⁹ R⁵⁰), then R⁴⁵ is not H or primary alkyl. In a third embodiment, when K and L are both O, and M is CH(OR⁴⁸), then R⁴⁶ and R⁴⁸ do not both comprise aziridines. In a fourth embodiment, when K and L are both O, and M is CH(OR⁴⁸), then R⁴⁵, R⁴⁶, and R⁴⁸ do not simultaneously comprise alkenyl ethers. In a fifth embodiment, when K and L are both O, and M is CH(OR⁴⁸), then R⁴⁵ and R⁴⁶ do not both comprise glycidyl ethers.

[0040] In a preferred embodiment of the invention, the active vitamin D compound has a reduced hypercalcemic effect as compared to vitamin D so that sufficient doses of the compound can be administered without inducing hypercalcemia in the animal. A reduced hypercalcemic effect is defined as an effect which is less than the hypercalcemic effect induced by administration of an equal dose of 1 α ,25-hydroxyvitamin D₃ (calcitriol). As an example, EB 1089 has a hypercalcemic effect which is 50% of the hypercalcemic effect of calcitriol. Additional active vitamin D compounds having a reduced hypercalcemic effect include Ro23-7553 and Ro24-5531 available from Hoffman LaRoche. Other examples of active vitamin D compounds having a reduced hypercalcemic effect can be found in U.S. Patent No. 4,717,721. Determining the hypercalcemic effect of an active vitamin D compound is routine in the art and can be carried out as disclosed in Hansen *et al.*, *Curr. Pharm. Des.* 6: 803-828 (2000).

[0041] The term "high dose pulse administration (HDP)" as used herein, refers to a regimen of administration of an active vitamin D compound to an animal which achieves the desired result of preventing, treating or ameliorating a GI disorder in the animal without inducing severe symptomatic hypercalcemia, *e.g.*, a dose of at least 3 μ g no more than once every three days.

[0042] The term "hypercalcemia" as used herein, refers to a medical condition in which the concentration of calcium ions in the plasma is greater than about 10.5 mg/dL in humans. Methods to determine the concentration of calcium

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ions in blood plasma are generally within the capability of a person of ordinary skill in the art.

[0043] The term "symptomatic hypercalcemia" as used herein, refers to one or more of the signs or symptoms associated with hypercalcemia. Early manifestations of hypercalcemia include weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, or metallic taste. Late manifestations include polydipsia, polyuria, weight loss, pancreatitis, photophobia, pruritis, renal dysfunction, aminotransferase elevation, hypertension, cardiac arrhythmias, psychosis, stupor, or coma.

[0044] The term "severe symptomatic hypercalcemia" as used herein, refers to a grade 3 or grade 4 toxicity level of hypercalcemia (*i.e.*, >12.6 mg/dL) as defined by the NCI common toxicity criteria and listed in U.S. Patent 6,521,608, which is incorporated by reference herein in its entirety.

[0045] In one embodiment of the invention, an active vitamin D compound is administered to an animal before, during and/or after chemotherapy or radiation therapy. The active vitamin D compound can be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, or more prior to the chemotherapy or radiation therapy. The active vitamin D compound can be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, or more after the chemotherapy or radiation therapy and continued for up to six months. In certain embodiments the active vitamin D compound is administered before, during, and after the chemotherapy or radiation therapy.

[0046] In one aspect of the invention, one or more therapeutic agents are administered to an animal in addition to the active vitamin D compound. The active vitamin D compound can be administered prior to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 3 weeks, 4 weeks or more), concurrently with, or after (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 3 weeks, 4 weeks or more) the administration of one or more therapeutic agents.

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[0047] In certain embodiments, the method of administering an active vitamin D compound in combination with one or more therapeutic agents may be repeated at least once. The method may be repeated as many times as necessary to achieve or maintain a therapeutic response, *e.g.*, from one to about ten times or more. With each repetition of the method the active vitamin D compound and the one or more therapeutic agents may be the same or different from that used in the previous repetition. Additionally, the time period of administration of the active vitamin D compound and the manner in which it is administered (*i.e.*, daily or HDPA) can vary from repetition to repetition.

[0048] When used, the one or more therapeutic agents are administered in doses known to one of skill in the art to prevent, treat, or ameliorate a GI or bladder disorder. The one or more therapeutic agents are administered in pharmaceutical compositions and by methods known to be effective. For example, the therapeutic agents may be administered systemically (*e.g.*, intravenously, orally) or locally (*e.g.*, intravesicle instillation).

[0049] The active vitamin D compound is preferably administered at a dose of about 0.1 μg to about 10 mg, *e.g.*, about 0.5 μg to about 1 mg, more preferably from about 15 μg to about 500 μg . In a specific embodiment, an effective amount of an active vitamin D compound is 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, or 10000 μg or more. In certain embodiments, an effective dose of an active vitamin D compound is between about 3 μg to about 10 mg, *e.g.*, between about 15 μg to about 1 mg, between about 30 μg to about 300 μg , between about 50 μg to about 220 μg , or between about 75 μg to about 200 μg . In certain embodiments, the methods of the invention comprise administering an active vitamin D compound in a dose of about 0.12 $\mu\text{g}/\text{kg}$ bodyweight to about 200 $\mu\text{g}/\text{kg}$ bodyweight. The compound may be administered by any route,

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including oral, intramuscular, intravenous, parenteral, rectal, nasal, topical, or transdermal.

[0050] If the active vitamin D compound is to be administered daily, the dose may be kept low, for example about 0.5 μg to about 5 μg , in order to avoid or diminish the induction of hypercalcemia. If the active vitamin D compound has a reduced hypercalcemic effect a higher daily dose may be administered without resulting in hypercalcemia, for example about 10 μg to about 20 μg or higher (up to about 50 μg to about 100 μg).

[0051] In a preferred embodiment of the invention, the active vitamin D compound is administered by HDPA so that high doses of the active vitamin D compound can be administered without inducing severe symptomatic hypercalcemia. HDPA refers to intermittently administering an active vitamin D compound on either a continuous intermittent dosing schedule or a non-continuous intermittent dosing schedule. High doses of active vitamin D compounds include doses greater than about 3 μg as discussed in the sections above. Therefore, in certain embodiments of the invention, the methods for the prevention, treatment, or amelioration of GI and bladder disorders encompass intermittently administering high doses of active vitamin D compounds. The frequency of the HDPA can be limited by a number of factors including, but not limited to, the pharmacokinetic parameters of the compound or formulation and the pharmacodynamic effects of the active vitamin D compound on the animal. For example, animals having impaired renal function may require less frequent administration of the active vitamin D compound because of the decreased ability of those animals to excrete calcium.

[0052] The following is exemplary only and merely serves to illustrate that the term HDPA can encompass any discontinuous administration regimen designed by a person of skill in the art.

[0053] In one example, the active vitamin D compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, every ten days, every two weeks, every three weeks, or every four weeks. The administration

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can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the active vitamin D compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the active vitamin D compound on the animal.

[0054] In another example, the active vitamin D compound can be administered once per week for three months.

[0055] In a preferred embodiment, the vitamin D compound can be administered once per week for three weeks of a four week cycle. After a one week period of rest, the active vitamin D compound can be administered under the same or different schedule.

[0056] In another example, the active vitamin D compound is administered once every 2, 3, or 4, weeks.

[0057] Further examples of dosing schedules that can be used in the methods of the present invention are provided in U.S. Patent No. 6,521,608.

[0058] The above-described administration schedules are provided for illustrative purposes only and should not be considered limiting. A person of skill in the art will readily understand that all active vitamin D compounds are within the scope of the invention and that the exact dosing and schedule of administration of the active vitamin D compounds can vary due to many factors.

[0059] The amount of a therapeutically effective dose of a pharmaceutical agent in the acute or chronic management of a disease or disorder may differ depending on factors including, but not limited to, the disease or disorder treated, the specific pharmaceutical agents and the route of administration. According to the methods of the invention, an effective dose of an active vitamin D compound is any dose of the compound effective to prevent, treat, or ameliorate a GI or bladder disorder. A high dose of an active vitamin D compound can be a dose from about 3 μ g to about 10 mg or any dose within this range as discussed above. The dose, dose frequency, duration, or any combination thereof, may also vary according to age, body weight, response, and the past medical history of the animal as well as the route of

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administration, pharmacokinetics, and pharmacodynamic effects of the pharmaceutical agents. These factors are routinely considered by one of skill in the art.

[0060] The rate of absorption and clearance of vitamin D compounds is affected by a variety of factors that are well known to persons of skill in the art. As discussed above, the pharmacokinetic properties of active vitamin D compounds limit the peak concentration of vitamin D compounds that can be obtained in the blood without inducing the onset of hypercalcemia. The rate and extent of absorption, distribution, binding or localization in tissues, biotransformation, and excretion of the active vitamin D compound can all affect the frequency at which the pharmaceutical agents can be administered.

[0061] In one embodiment of the invention, an active vitamin D compound is administered at a dose sufficient to achieve peak plasma concentrations of the active vitamin D compound of about 0.1 nM to about 1000 nM, *e.g.*, about 0.1 nM to about 25 nM. In certain embodiments, the methods of the invention comprise administering the active vitamin D compound in a dose that achieves peak plasma concentrations of 0.1 nM, 0.2 nM, 0.3 nM, 0.4 nM, 0.5 nM, 0.6 nM, 0.7 nM, 0.8 nM, 0.9 nM, 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM, 10 nM, 12.5 nM, 15 nM, 17.5 nM, 20 nM, 22.5 nM, 25 nM, 30 nM, 35 nM, 40 nM, 45 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 150 nM, 200 nM, 250 nM, 300 nM, 350 nM, 400 nM, 450 nM, 500 nM, 550 nM, 600 nM, 650 nM, 700 nM, 750 nM, 800 nM, 850 nM, 900 nM, 950 nM or 1000 nM or any range of concentrations therein. In other embodiments, the active vitamin D compound is administered in a dose that achieves peak plasma concentrations of the active vitamin D compound exceeding about 0.5 nM, *e.g.*, about 0.5 nM to about 1000 nM, about 0.5 nM to about 100 nM, about 0.5 nM to about 25 nM, about 5 nM to about 20 nM, or about 10 nM to about 15 nM.

[0062] In another preferred embodiment, the active vitamin D compound is administered at a dose of at least about 0.12 µg/kg bodyweight, more preferably at a dose of at least about 0.5 µg/kg bodyweight.

[0063] One of skill in the art will recognize that these standard doses are for an average sized adult of approximately 70 kg and can be adjusted for the factors routinely considered as stated above.

[0064] In certain embodiments, the methods of the invention further comprise administering a dose of an active vitamin D compound that achieves peak plasma concentrations rapidly, *e.g.*, within four hours. In further embodiments, the methods of the invention comprise administering a dose of an active vitamin D compound that is eliminated quickly, *e.g.*, with an elimination half-life of less than 12 hours.

[0065] While obtaining high concentrations of the active vitamin D compound is beneficial, it must be balanced with clinical safety, *e.g.*, hypercalcemia. Thus, in one aspect of the invention, the methods of the invention encompass HDPA of active vitamin D compounds to an animal before, during, or after chemotherapy or radiation therapy and monitoring the animal for symptoms associated with hypercalcemia. Such symptoms include calcification of soft tissues (*e.g.*, cardiac tissue), increased bone density, and hypercalcemic nephropathy. In still another embodiment, the methods of the invention encompass HDPA of an active vitamin D compound to an animal before, during, or after chemotherapy or radiation therapy and monitoring the calcium plasma concentration of the animal to ensure that the calcium plasma concentration is less than about 11.5 mg/dL.

[0066] In certain embodiments, high blood levels of vitamin D compounds can be safely obtained in conjunction with reducing the transport of calcium into the blood. In one embodiment, higher active vitamin D compound concentrations are safely obtainable without the onset of hypercalcemia when administered in conjunction with a reduced calcium diet. In one example, the calcium can be trapped by an adsorbent, absorbent, ligand, chelate, or other binding moiety that cannot be transported into the blood through the small intestine. In another example, the rate of osteoclast activation can be inhibited by administering, for example, a bisphosphonate such as, *e.g.*, zoledronate, pamidronate, or alendronate, or a corticosteroid such as, *e.g.*, dexamethasone or prednisone, in conjunction with the active vitamin D compound.

[0067] In certain embodiments, high blood levels of active vitamin D compounds are safely obtained in conjunction with maximizing the rate of clearance of calcium. In one example, calcium excretion can be increased by ensuring adequate hydration and salt intake. In another example, diuretic therapy can be used to increase calcium excretion.

[0068] The doses of the vitamin D analogs and vitamin D mimics may be adjusted proportionate to the ratio of the efficacy index to the calcemic index according to the formula:

$$\text{Dose} = \text{CalcitriolDose} \times (EI \div CI)$$

where Dose is the analog or mimic dose, calcitriolDose is calcitriol dose, EI is the analog or mimic efficacy index and CI is the analog or mimic calcemic index, wherein the term "efficacy index" is the ratio of the concentration of the vitamin D analog or mimic to the concentration of calcitriol at equivalent potency. Thus, the efficacy index is a fraction less than one when the vitamin D analog or mimic is less potent than calcitriol. EI is a number greater than one when calcitriol is less potent than the vitamin D analog or mimic. The "calcemic index" of a drug is a measure of the relative ability of the drug to generate a calcemic response as reported in Bouillon *et al.*, *Endocrine Rev.* 16:200 (1995). A calcemic index of 1 corresponds to the relative calcemic activity of calcitriol. A calcemic index of about 0.01 corresponds to the calcemic activity of a drug with approximately 100 times less calcemic activity than calcitriol. A calcemic index of 0.5 would correspond to a drug having approximately half the calcemic activity of calcitriol. The calcemic index of a drug can vary depending on the assay conducted, *e.g.*, whether one is measuring stimulation of intestinal calcium absorption (a process by which dietary calcium enters into the physiological processes to contribute to the skeletal growth of the organism and to the maintenance of calcium homeostasis) or bone calcium mobilizing activity (a process by which the bone matrix acts as an exchangeable reservoir for calcium). See U.S. Patent No. 6,521,608 for further detail.

[0069] The active vitamin D compound may be administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier,

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wherein the active vitamin D compound is present in an amount which is effective to achieve its intended purpose, *i.e.*, to have the desired effect of preventing, treating, or ameliorating a GI or bladder disorder in a patient receiving chemotherapy or radiation therapy. The pharmaceutical composition may further comprise one or more excipients, diluents or any other components known to persons of skill in the art and germane to the methods of formulation of the present invention. The pharmaceutical composition may additionally comprise other compounds typically used as adjuncts during prevention, treatment, or amelioration of GI and bladder disorders.

[0070] The term "pharmaceutical composition" as used herein is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, *e.g.*, where oral administration is foreseen, acceptable for oral use and, where topical administration is foreseen, topically acceptable.

[0071] The pharmaceutical composition can be prepared in single unit dosage forms. The dosage forms are suitable for oral, mucosal (nasal, sublingual, vaginal, buccal, rectal), parenteral (intravenous, intramuscular, intraarterial), or topical administration. Preferred dosage forms of the present invention include oral dosage forms and intravenous dosage forms. In other embodiments, the dosage forms are suitable for local administration, *e.g.*, in the form of a mouth wash, gel or slow release lozenge in the case of oral mucositis, in a form that coats the surface of the GI tract for GI mucositis, or in a form suitable for intravesicle instillation for cystitis.

[0072] Intravenous forms include, but are not limited to, bolus and drip injections. In preferred embodiments, the intravenous dosage forms are sterile or capable of being sterilized prior to administration to a subject since they typically bypass the subject's natural defenses against contaminants. Examples of intravenous dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles including, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles including, but not limited to, ethyl alcohol, polyethylene glycol and

polypropylene glycol; and non-aqueous vehicles including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate and benzyl benzoate.

[0073] In a preferred embodiment of the invention, the pharmaceutical compositions comprising active vitamin D compounds are emulsion pre-concentrate formulations. The compositions of the invention meet or substantially reduce the difficulties associated with active vitamin D compound therapy hitherto encountered in the art including, in particular, undesirable pharmacokinetic parameters of the compound upon administration to a patient.

[0074] According to one aspect of the present invention, a pharmaceutical composition is provided comprising (a) a lipophilic phase component, (b) one or more surfactants, (c) an active vitamin D compound; wherein said composition is an emulsion pre-concentrate, which upon dilution with water, in a water to composition ratio of about 1:1 or more of said water, forms an emulsion having an absorbance of greater than 0.3 at 400 nm. The pharmaceutical composition of the invention may further comprise a hydrophilic phase component.

[0075] In another aspect of the invention, a pharmaceutical emulsion composition is provided comprising water (or other aqueous solution) and an emulsion pre-concentrate.

[0076] The term "emulsion pre-concentrate," as used herein, is intended to mean a system capable of providing an emulsion upon contacting with, *e.g.*, water. The term "emulsion," as used herein, is intended to mean a colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. The term "emulsion" is intended to encompass both conventional emulsions, as understood by those skilled in the art, as well as "sub-micron droplet emulsions," as defined immediately below.

[0077] The term "sub-micron droplet emulsion," as used herein is intended to mean a dispersion comprising water and organic components including hydrophobic (lipophilic) organic components, wherein the droplets or particles

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formed from the organic components have an average maximum dimension of less than about 1000 nm.

[0078] Sub-micron droplet emulsions are identifiable as possessing one or more of the following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, *e.g.*, in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability and they are monophasic.

[0079] The particles of a sub-micron droplet emulsion may be spherical, though other structures are feasible, *e.g.* liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, sub-micron droplet emulsions comprise droplets or particles having a maximum dimension (*e.g.*, average diameter) of between about 50 nm to about 1000 nm, and preferably between about 200 nm to about 300 nm.

[0080] The pharmaceutical compositions of the present invention will generally form an emulsion upon dilution with water. The emulsion will form according to the present invention upon the dilution of an emulsion pre-concentrate with water in a water to composition ratio of about 1:1 or more of said water. According to the present invention, the ratio of water to composition can be, *e.g.*, between 1:1 and 5000:1. For example, the ratio of water to composition can be about 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 200:1, 300:1, 500:1, 1000:1, or 5000:1. The skilled artisan will be able to readily ascertain the particular ratio of water to composition that is appropriate for any given situation or circumstance.

[0081] According to the present invention, upon dilution of said emulsion pre-concentrate with water, an emulsion will form having an absorbance of greater than 0.3 at 400 nm. The absorbance at 400 nm of the emulsions formed upon 1:100 dilution of the emulsion pre-concentrates of the present invention can be, *e.g.*, between 0.3 and 4.0. For example, the absorbance at 400 nm can be about 0.4, 0.5, 0.6, 1.0, 1.2, 1.6, 2.0, 2.2, 2.4, 2.5, 3.0, or 4.0. Methods for determining the absorbance of a liquid solution are well known by those in the art. The skilled artisan will be able to ascertain and adjust the relative

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proportions of the ingredients of the emulsion pre-concentrates of the invention in order to obtain, upon dilution with water, an emulsion having any particular absorbance encompassed within the scope of the invention.

[0082] The pharmaceutical compositions of the present invention can be, *e.g.*, in a solid, semi-solid, or liquid formulation. Semi-solid formulations of the present invention can be any semi-solid formulation known by those of ordinary skill in the art, including, *e.g.*, gels, pastes, creams and ointments.

[0083] The pharmaceutical compositions of the present invention comprise a lipophilic phase component. Suitable components for use as lipophilic phase components include any pharmaceutically acceptable solvent which is non-miscible with water. Such solvents will appropriately be devoid or substantially devoid of surfactant function.

[0084] The lipophilic phase component may comprise mono-, di- or triglycerides. Mono-, di- and triglycerides that may be used within the scope of the invention include those that are derived from C₆, C₈, C₁₀, C₁₂, C₁₄, C₁₆, C₁₈, C₂₀ and C₂₂ fatty acids. Exemplary diglycerides include, in particular, diolein, dipalmitolein, and mixed caprylin-caprin diglycerides. Preferred triglycerides include vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, synthetic triglycerides, modified triglycerides, fractionated triglycerides, medium and long-chain triglycerides, structured triglycerides, and mixtures thereof.

[0085] Among the above-listed triglycerides, preferred triglycerides include: almond oil; babassu oil; borage oil; blackcurrant seed oil; canola oil; castor oil; coconut oil; corn oil; cottonseed oil; evening primrose oil; grapeseed oil; groundnut oil; mustard seed oil; olive oil; palm oil; palm kernel oil; peanut oil; rapeseed oil; safflower oil; sesame oil; shark liver oil; soybean oil; sunflower oil; hydrogenated castor oil; hydrogenated coconut oil; hydrogenated palm oil; hydrogenated soybean oil; hydrogenated vegetable oil; hydrogenated cottonseed and castor oil; partially hydrogenated soybean oil; partially soy and cottonseed oil; glyceryl tricaproate; glyceryl tricaprylate; glyceryl tricaprinate; glyceryl triundecanoate; glyceryl trilaurate; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; glyceryl tricaprylate/caprinate; glyceryl

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tricaprylate/caprate/laurate; glyceryl tricaprylate/caprate/linoleate; and glyceryl tricaprylate/caprate/stearate.

[0086] A preferred triglyceride is the medium chain triglyceride available under the trade name LABRAFAC CC. Other preferred triglycerides include neutral oils, *e.g.*, neutral plant oils, in particular fractionated coconut oils such as known and commercially available under the trade name MIGLYOL, including the products: MIGLYOL 810; MIGLYOL 812; MIGLYOL 818; and CAPTEX 355.

[0087] Also suitable are caprylic-capric acid triglycerides such as known and commercially available under the trade name MYRITOL, including the product MYRITOL 813. Further suitable products of this class are CAPMUL MCT, CAPTEX 200, CAPTEX 300, CAPTEX 800, NEOBEE M5 and MAZOL 1400.

[0088] Especially preferred as lipophilic phase component is the product MIGLYOL 812. (*See* U.S. Patent No. 5,342,625).

[0089] Pharmaceutical compositions of the present invention may further comprise a hydrophilic phase component. The hydrophilic phase component may comprise, *e.g.*, a pharmaceutically acceptable C₁₋₅ alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol. Suitable hydrophilic phase components include, *e.g.*, di- or partial-, especially partial-, -ethers of mono- or poly-, especially mono- or di-, -oxy-alkanediols comprising from 2 to 12, especially 4 carbon atoms. Preferably the mono- or poly-oxy-alkanediol moiety is straight-chained. Exemplary hydrophilic phase components for use in relation to the present invention are those known and commercially available under the trade names TRANSCUTOL and COLYCOFUROL. (*See* U.S. Patent No. 5,342,625).

[0090] In an especially preferred embodiment, the hydrophilic phase component comprises 1,2-propyleneglycol.

[0091] The hydrophilic phase component of the present invention may of course additionally include one or more additional ingredients. Preferably, however, any additional ingredients will comprise materials in which the active vitamin D compound is sufficiently soluble, such that the efficacy of the

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hydrophilic phase as an active vitamin D compound carrier medium is not materially impaired. Examples of possible additional hydrophilic phase components include lower (*e.g.*, C₁₋₅) alkanols, in particular ethanol.

[0092] Pharmaceutical compositions of the present invention also comprise one or more surfactants. Surfactants that can be used in conjunction with the present invention include hydrophilic or lipophilic surfactants, or mixtures thereof. Especially preferred are non-ionic hydrophilic and non-ionic lipophilic surfactants.

[0093] Suitable hydrophilic surfactants include reaction products of natural or hydrogenated vegetable oils and ethylene glycol, *i.e.* polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, *e.g.*, by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, *e.g.*, in a molar ratio of from about 1:35 to about 1:60, with optional removal of free polyethyleneglycol components from the product, *e.g.*, in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819.

[0094] Suitable hydrophilic surfactants for use in the present pharmaceutical compounds also include polyoxyethylene-sorbitan-fatty acid esters, *e.g.*, mono- and trilauryl, palmityl, stearyl and oleyl esters, *e.g.*, of the type known and commercially available under the trade name TWEEN; including the products:

TWEEN 20 (polyoxyethylene(20)sorbitanmonolaurate),
TWEEN 40 (polyoxyethylene(20)sorbitanmonopalmitate),
TWEEN 60 (polyoxyethylene(20)sorbitanmonostearate),
TWEEN 80 (polyoxyethylene(20)sorbitanmonooleate),
TWEEN 65 (polyoxyethylene(20)sorbitantristearate),
TWEEN 85 (polyoxyethylene(20)sorbitantrioleate),
TWEEN 21 (polyoxyethylene(4)sorbitanmonolaurate),
TWEEN 61 (polyoxyethylene(4)sorbitanmonostearate), and
TWEEN 81 (polyoxyethylene(5)sorbitanmonooleate).

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- [0095] Especially preferred products of this class for use in the compositions of the invention are the above products TWEEN 40 and TWEEN 80. (*See* Hauer, *et al.*, U.S. Patent No. 5,342,625).
- [0096] Also suitable as hydrophilic surfactants for use in the present pharmaceutical compounds are polyoxyethylene alkylethers; polyoxyethylene glycol fatty acid esters, for example polyoxyethylene stearic acid esters; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and, *e.g.*, fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; polyoxyethylene-polyoxypropylene co-polymers; polyoxyethylene-polyoxypropylene block co-polymers; dioctylsuccinate, dioctylsodiumsulfosuccinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate; phospholipids, in particular lecithins such as, *e.g.*, soya bean lecithins; propylene glycol mono- and di-fatty acid esters such as, *e.g.*, propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate, and, especially preferred, propylene glycol caprylic-capric acid diester; and bile salts, *e.g.*, alkali metal salts, for example sodium taurocholate.
- [0097] Suitable lipophilic surfactants include alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid esters of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; trans-esterified vegetable oils; sterols; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

[0098] Suitable lipophilic surfactants for use in the present pharmaceutical compounds also include trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Such trans-esterification products are known in the art and may be obtained *e.g.*, in accordance with the general procedures described in U.S. Patent No. 3,288,824. They include trans-esterification products of various natural (*e.g.*, non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred are products obtained by trans-esterification of 2 molar parts of a natural vegetable oil triglyceride with one molar part of polyethylene glycol (*e.g.*, having an average molecular weight of from 200 to 800). Various forms of trans-esterification products of the defined class are known and commercially available under the trade name LABRAFIL.

[0099] Additional lipophilic surfactants that are suitable for use with the present pharmaceutical compositions include oil-soluble vitamin derivatives, *e.g.*, tocopherol PEG-1000 succinate ("vitamin E TPGS").

[0100] Also suitable as lipophilic surfactants for use in the present pharmaceutical compounds are mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol; sorbitan fatty acid esters; pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite- -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentaerythrite-fatty acid esters; monoglycerides, *e.g.*, glycerol monooleate, glycerol monopalmitate and glycerol monostearate; glycerol triacetate or (1,2,3)-triacetin; and sterols and derivatives thereof, for example cholesterol and derivatives thereof, in particular phytosterols, *e.g.*, products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof.

[0101] It is understood by those of ordinary skill in the art that several commercial surfactant compositions contain small to moderate amounts of triglycerides, typically as a result of incomplete reaction of a triglyceride starting material in, for example, a trans-esterification reaction. Thus, the

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surfactants that are suitable for use in the present pharmaceutical compositions include those surfactants that contain a triglyceride. Examples of commercial surfactant compositions containing triglycerides include some members of the surfactant families GELUCIRES, MAISINES, and IMWITORS. Specific examples of these compounds are GELUCIRE 44/14 (saturated polyglycolized glycerides); GELUCIRE 50/13 (saturated polyglycolized glycerides); GELUCIRE 53/10 (saturated polyglycolized glycerides); GELUCIRE 33/01 (semi-synthetic triglycerides of C₈-C₁₈ saturated fatty acids); GELUCIRE 39/01 (semi-synthetic glycerides); other GELUCIRES, such as 37/06, 43/01, 35/10, 37/02, 46/07, 48/09, 50/02, 62/05, *etc.*; MAISINE 35-I (linoleic glycerides); and IMWITOR 742 (caprylic/capric glycerides). (*See* U.S. Patent No. 6,267,985).

[0102] Still other commercial surfactant compositions having significant triglyceride content are known to those skilled in the art. It should be appreciated that such compositions, which contain triglycerides as well as surfactants, may be suitable to provide all or part of the lipophilic phase component of the of the present invention, as well as all or part of the surfactants.

[0103] The relative proportion of ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned. The relative proportions will also vary depending on the particular function of ingredients in the composition. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, *e.g.*, in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of a person of ordinary skill in the art. All indicated proportions and relative weight ranges described below are accordingly to be understood as being indicative of preferred or individually inventive teachings only and not as limiting the invention in its broadest aspect.

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[0104] The lipophilic phase component of the invention will suitably be present in an amount of from about 30% to about 90% by weight based upon the total weight of the composition. Preferably, the lipophilic phase component is present in an amount of from about 50% to about 85% by weight based upon the total weight of the composition.

[0105] The surfactant or surfactants of the invention will suitably be present in an amount of from about 1% to 50% by weight based upon the total weight of the composition. Preferably, the surfactant(s) is present in an amount of from about 5% to about 40% by weight based upon the total weight of the composition.

[0106] The amount of active vitamin D compound in compositions of the invention will of course vary, *e.g.*, depending on the intended route of administration and to what extent other components are present. In general, however, the active vitamin D compound of the invention will suitably be present in an amount of from about 0.005% to 20% by weight based upon the total weight of the composition. Preferably, the active vitamin D compound is present in an amount of from about 0.01% to 15% by weight based upon the total weight of the composition.

[0107] The hydrophilic phase component of the invention will suitably be present in an amount of from about 2% to about 20% by weight based upon the total weight of the composition. Preferably, the hydrophilic phase component is present in an amount of from about 5% to 15% by weight based upon the total weight of the composition.

[0108] The pharmaceutical composition of the invention may be in a semisolid formulation. Semisolid formulations within the scope of the invention may comprise, *e.g.*, a lipophilic phase component present in an amount of from about 60% to about 80% by weight based upon the total weight of the composition, a surfactant present in an amount of from about 5% to about 35% by weight based upon the total weight of the composition, and an active vitamin D compound present in an amount of from about 0.01% to about 15% by weight based upon the total weight of the composition.

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[0109] The pharmaceutical compositions of the invention may be in a liquid formulation. Liquid formulations within the scope of the invention may comprise, *e.g.*, a lipophilic phase component present in an amount of from about 50% to about 60% by weight based upon the total weight of the composition, a surfactant present in an amount of from about 4% to about 25% by weight based upon the total weight of the composition, an active vitamin D compound present in an amount of from about 0.01% to about 15% by weight based upon the total weight of the composition, and a hydrophilic phase component present in an amount of from about 5% to about 10% by weight based upon the total weight of the composition.

[0110] Additional compositions that may be used include the following, wherein the percentage of each component is by weight based upon the total weight of the composition excluding the active vitamin D compound:

- | | | |
|----|----------------|------------|
| a. | Gelucire 44/14 | about 50% |
| | Miglyol 812 | about 50%; |
| b. | Gelucire 44/14 | about 50% |
| | Vitamin E TPGS | about 10% |
| | Miglyol 812 | about 40%; |
| c. | Gelucire 44/14 | about 50% |
| | Vitamin E TPGS | about 20% |
| | Miglyol 812 | about 30%; |
| d. | Gelucire 44/14 | about 40% |
| | Vitamin E TPGS | about 30% |
| | Miglyol 812 | about 30%; |
| e. | Gelucire 44/14 | about 40% |
| | Vitamin E TPGS | about 20% |
| | Miglyol 812 | about 40%; |

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- | | | |
|----|----------------|------------|
| f. | Gelucire 44/14 | about 30% |
| | Vitamin E TPGS | about 30% |
| | Miglyol 812 | about 40%; |
| g. | Gelucire 44/14 | about 20% |
| | Vitamin E TPGS | about 30% |
| | Miglyol 812 | about 50%; |
| h. | Vitamin E TPGS | about 50% |
| | Miglyol 812 | about 50%; |
| i. | Gelucire 44/14 | about 60% |
| | Vitamin E TPGS | about 25% |
| | Miglyol 812 | about 15%; |
| j. | Gelucire 50/13 | about 30% |
| | Vitamin E TPGS | about 5% |
| | Miglyol 812 | about 65%; |
| k. | Gelucire 50/13 | about 50% |
| | Miglyol 812 | about 50%; |
| l. | Gelucire 50/13 | about 50% |
| | Vitamin E TPGS | about 10% |
| | Miglyol 812 | about 40%; |
| m. | Gelucire 50/13 | about 50% |
| | Vitamin E TPGS | about 20% |
| | Miglyol 812 | about 30%; |
| n. | Gelucire 50/13 | about 40% |

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	Vitamin E TPGS	about 30%
	Miglyol 812	about 30%;
o.	Gelucire 50/13	about 40%
	Vitamin E TPGS	about 20%
	Miglyol 812	about 40%;
p.	Gelucire 50/13	about 30%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 40%;
q.	Gelucire 50/13	about 20%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 50%;
r.	Gelucire 50/13	about 60%
	Vitamin E TPGS	about 25%
	Miglyol 812	about 15%;
s.	Gelucire 44/14	about 50%
	PEG 4000	about 50%;
t.	Gelucire 50/13	about 50%
	PEG 4000	about 50%;
u.	Vitamin E TPGS	about 50%
	PEG 4000	about 50%;
v.	Gelucire 44/14	about 33.3%
	Vitamin E TPGS	about 33.3%
	PEG 4000	about 33.3%;

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w.	Gelucire 50/13	about 33.3%
	Vitamin E TPGS	about 33.3%
	PEG 4000	about 33.3%;
x.	Gelucire 44/14	about 50%
	Vitamin E TPGS	about 50%;
y.	Gelucire 50/13	about 50%
	Vitamin E TPGS	about 50%;
z.	Vitamin E TPGS	about 5%
	Miglyol 812	about 95%;
aa.	Vitamin E TPGS	about 5%
	Miglyol 812	about 65%
	PEG 4000	about 30%;
ab.	Vitamin E TPGS	about 10%
	Miglyol 812	about 90%;
ac.	Vitamin E TPGS	about 5%
	Miglyol 812	about 85%
	PEG 4000	about 10%; and
ad.	Vitamin E TPGS	about 10%
	Miglyol 812	about 80%
	PEG 4000	about 10%.

[0111] In one embodiment of the invention, the pharmaceutical compositions comprise an active vitamin D compound, a lipophilic component, and a surfactant. The lipophilic component may be present in any percentage from about 1% to about 100%. The lipophilic component may be present at about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,

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25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%. The surfactant may be present in any percentage from about 1% to about 100%. The surfactant may be present at about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%. In one embodiment, the lipophilic component is MIGLYOL 812 and the surfactant is vitamin E TPGS. In preferred embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812 and about 50% vitamin E TPGS, about 90% MIGLYOL 812 and about 10% vitamin E TPGS, or about 95% MIGLYOL 812 and about 5% vitamin E TPGS.

[0112] In another embodiment of the invention, the pharmaceutical compositions comprise an active vitamin D compound and a lipophilic component, *e.g.*, around 100% MIGLYOL 812.

[0113] In a preferred embodiment, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, and small amounts of BHA and BHT (*e.g.*, less than 1% each). This formulation has been shown to be unexpectedly stable, both chemically and physically (see Example 3). The enhanced stability provides the compositions with a longer shelf life. Importantly, the stability also allows the compositions to be stored at room temperature, thereby avoiding the complication and cost of storage under refrigeration. Additionally, this composition is suitable for oral administration and has been shown to be capable of solubilizing high doses of active vitamin D compound, thereby enabling high dose pulse administration of active vitamin D compounds for the treatment of hyperproliferative diseases and other disorders.

[0114] In certain embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, and about 0.01% to

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about 0.50% each of BHA and BHT. In other embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, and about 0.05% to about 0.35% each of BHA and BHT. In certain embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.35% BHA, and about 0.10% BHT.

[0115] Additional compositions that may be used include the following, wherein the percentage of each component is by weight based upon the total weight of the composition excluding the active vitamin D compound or a mimic thereof:

- | | | |
|----|----------------|--------------|
| a. | MIGLYOL 812 | about 100% |
| | BHA | about 0.05% |
| | BHT | about 0.05%; |
| b. | MIGLYOL 812 | about 100% |
| | BHA | about 0.35% |
| | BHT | about 0.10%; |
| c. | MIGLYOL 812 | about 50% |
| | Vitamin E TPGS | about 50% |
| | BHA | about 0.05% |
| | BHT | about 0.05%; |
| d. | MIGLYOL 812 | about 50% |
| | Vitamin E TPGS | about 50% |
| | BHT | about 0.10%; |
| e. | MIGLYOL 812 | about 50% |
| | Vitamin E TPGS | about 50% |
| | BHA | about 0.35%; |

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- | | | |
|----|----------------|------------------|
| f. | MIGLYOL 812 | about 50% |
| | Vitamin E TPGS | about 50% |
| | BHA | about 0.35% |
| | BHT | about 0.10%; and |
| | | |
| g. | MIGLYOL 812 | about 50% |
| | Vitamin E TPGS | about 50% |
| | BHA | about 0.28% |
| | BHT | about 0.08%. |

[0116] It will be understood by those of skill in the art that the formulations of the invention comprising a lipophilic component and a surfactant in amounts that total about 100% (*e.g.*, about 50% lipophilic component and about 50% surfactant) provide adequate room for the active vitamin D compound and additives (*e.g.*, antioxidants) which are present in the formulation in small amounts, each generally present at less than 1% by weight.

[0117] The pharmaceutical compositions comprising the active vitamin D compound of the present invention may further comprise one or more additives. Additives that are well known in the art include, *e.g.*, detackifiers, anti-foaming agents, buffering agents, antioxidants (*e.g.*, ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, *e.g.*, α -tocopherol (vitamin E)), preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired. For example, antioxidants may be present in an amount of from about 0.05% to about 0.35% by weight based upon the total weight of the composition.

[0118] The additive may also comprise a thickening agent. Suitable thickening agents may be those known and employed in the art, including, *e.g.*, pharmaceutically acceptable polymeric materials and inorganic thickening agents. Exemplary thickening agents for use in the present pharmaceutical

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compositions include polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid/methacrylic acid resins; celluloses and cellulose derivatives including: alkyl celluloses, *e.g.*, methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses, *e.g.*, hydroxypropyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, *e.g.*, cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl-celluloses; polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers; polyvinyl resins, *e.g.*, including polyvinylacetates and alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, *e.g.*, alginic acid, and salts thereof, *e.g.*, sodium alginates; and inorganic thickening agents such as atapulgite, bentonite and silicates including hydrophilic silicon dioxide products, *e.g.*, alkylated (for example methylated) silica gels, in particular colloidal silicon dioxide products.

[0119] Such thickening agents as described above may be included, *e.g.*, to provide a sustained release effect. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required and is generally less preferred. Use of thickening agents is, on the other hand, indicated, *e.g.*, where topical application is foreseen.

[0120] Compositions in accordance with the present invention may be employed for administration in any appropriate manner, *e.g.*, orally, *e.g.*, in unit dosage form, for example in a solution, in hard or soft encapsulated form including gelatin encapsulated form, parenterally or topically, *e.g.*, for application to the skin, for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch or the like, as a coating for a medical device, *e.g.*, a stent, or for ophthalmic application, for example in the form of an eye-drop, -lotion or -gel formulation. Readily flowable forms, for example solutions and emulsions, may also be employed *e.g.*, for intralesional injection, or may be administered rectally, *e.g.*, as an enema.

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Forms for local administration may also be employed, *e.g.*, mouth wash, mouth rinse, gel, or lozenge for administration to the oral mucosa.

[0121] When the composition of the present invention is formulated in unit dosage form, the active vitamin D compound will preferably be present in an amount of between 1 and 1000 μg per unit dose. More preferably, the amount of active vitamin D compound per unit dose will be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 μg or any amount therein. In one embodiment, the amount of active vitamin D compound per unit dose will be about 5 μg to about 180 μg , more preferably about 10 μg to about 135 μg , more preferably about 45 μg . In one embodiment, the unit dosage form comprises 45, 90, 135, or 180 μg of calcitriol.

[0122] When the unit dosage form of the composition is a capsule, the total quantity of ingredients present in the capsule is preferably about 10-1000 μL . More preferably, the total quantity of ingredients present in the capsule is about 100-300 μL . In another embodiment, the total quantity of ingredients present in the capsule is preferably about 10-1500 mg, preferably about 100-1000 mg. In one embodiment, the total quantity is about 225, 450, 675, or 900 mg. In one embodiment, the unit dosage form is a capsule comprising 45, 90, 135, or 180 μg of calcitriol.

[0123] Animals which may be treated according to the present invention include all animals which may benefit from administration of the compounds of the present invention. Such animals include humans, pets such as dogs and cats, and veterinary animals such as cows, pigs, sheep, goats and the like.

[0124] The following examples are illustrative, but not limiting, of the methods of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in medical treatment and pharmaceutical science and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

PREPARATION OF SEMI-SOLID CALCITRIOL FORMULATIONS

[0125] Five semi-solid calcitriol formulations (SS1-SS5) were prepared containing the ingredients listed in Table 1. The final formulation contains 0.0208 mg calcitriol per gram of semi-solid formulation.

TABLE 1: Composition of Semi-Solid Calcitriol Formulation

Ingredients	SS1	SS2	SS3	SS4	SS5
Calcitriol	0.0208	0.0208	0.0208	0.0208	0.0208
Miglyol 812	80.0	0	65.0	0	79.0
Captex 200	0	82.0	0	60.0	0
Labrafac CC	0	0	0	0	12.0
Vitamin-E TPGS	20.0	18.0	5.0	5.0	9.0
Labrifil M	0	0	0	0	0
Gelucire 44/14	0	0	30.0	35.0	0
BHT	0.05	0.05	0.05	0.05	0.05
BHA	0.05	0.05	0.05	0.05	0.05

Amounts shown are in grams.

1. Preparation of Vehicles

[0126] One hundred gram quantities of the five semi-solid calcitriol formulations (SS1-SS5) listed in Table 1 were prepared as follows.

[0127] The listed ingredients, except for calcitriol, were combined in a suitable glass container and mixed until homogenous. Vitamin E TPGS and GELUCIRE 44/14 were heated and homogenized at 60°C prior to weighing and adding into the formulation.

2. Preparation of Active Formulations

[0128] The semi-solid vehicles were heated and homogenized at $\leq 60^\circ\text{C}$. Under subdued light, 12 ± 1 mg of calcitriol was weighed out into separate glass bottles with screw caps, one bottle for each formulation. (Calcitriol is light sensitive; subdued light/red light should be used when working with calcitriol/calcitriol formulations.) The exact weight was recorded to 0.1 mg.

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The caps were then placed on the bottles as soon as the calcitriol had been placed into the bottles. Next, the amount of each vehicle required to bring the concentration to 0.208 mg/g was calculated using the following formula:

$$C_w/0.208 = \text{required weight of vehicle}$$

Where C_w = weight of calcitriol, in mg, and

0.208 = final concentration of calcitriol (mg/g).

[0129] Finally, the appropriate amount of each vehicle was added to the respective bottle containing the calcitriol. The formulations were heated ($\leq 60^\circ\text{C}$) while being mixed to dissolve the calcitriol.

EXAMPLE 2

PREPARATION OF ADDITIONAL FORMULATIONS

[0130] Following the method of Example 1, twelve different formulations for calcitriol were prepared containing the ingredients listed in Table 2.

TABLE 2: Composition Formulations

Ingred- ients	1	2	3	4	5	6	7	8	9	10	11	12
Miglyol 812N	95	65	90	85	80	95	65	90	85	80	50	0
Vitamin E TPGS	5	5	10	5	10	5	5	10	5	10	50	50
PEG 4000	0	30	0	10	10	0	30	0	10	10	0	50
BHA	0.05	0.05	0.05	0.05	0.05	0.35	0.35	0.35	0.35	0.35	0.35	0.35
BHT	0.05	0.05	0.05	0.05	0.05	0.35	0.35	0.35	0.35	0.35	0.35	0.35

Amounts shown are percentages.

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EXAMPLE 3

STABLE UNIT DOSE FORMULATIONS

[0131] Formulations of calcitriol were prepared to yield the compositions in Table 3. The Vitamin E TPGS was warmed to approximately 50°C and mixed in the appropriate ratio with MIGLYOL 812. BHA and BHT were added to each formulation to achieve 0.35% w/w of each in the final preparations.

TABLE 3: Calcitriol formulations

Formulation #	MIGLYOL (% wt/wt)	Vitamin E TPGS (% wt/wt)
1	100	0
2	95	5
3	90	10
4	50	50

[0132] After formulation preparation, Formulations 2-4 were heated to approximately 50°C and mixed with calcitriol to produce 0.1 µg calcitriol/mg total formulation. The formulations containing calcitriol were then added (~250 µL) to a 25 mL volumetric flask and deionized water was added to the 25 mL mark. The solutions were then vortexed and the absorbance of each formulation was measured at 400 nm immediately after mixing (initial) and up to 10 min after mixing. As shown in Table 4, all three formulations produced an opalescent solution upon mixing with water. Formulation 4 appeared to form a stable suspension with no observable change in absorbance at 400 nm after 10 min.

TABLE 4: Absorption of formulations suspended in water

Formulation #	Absorbance at 400 nm	
	Initial	10 min
2	0.7705	0.6010
3	1.2312	1.1560
4	3.1265	3.1265

[0133] To further assess the formulations of calcitriol, a solubility study was conducted to evaluate the amount of calcitriol soluble in each formulation.

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Calcitriol concentrations from 0.1 to 0.6 μg calcitriol/mg formulation were prepared by heating the formulations to 50°C followed by addition of the appropriate mass of calcitriol. The formulations were then allowed to cool to room temperature and the presence of undissolved calcitriol was determined by a light microscope with and without polarizing light. For each formulation, calcitriol was soluble at the highest concentration tested, 0.6 μg calcitriol/mg formulation.

[0134] A 45 μg calcitriol dose is currently being used in Phase 2 human clinical trials. To develop a capsule with this dosage each formulation was prepared with 0.2 μg calcitriol/mg formulation and 0.35% w/w of both BHA and BHT. The bulk formulation mixtures were filled into Size 3 hard gelatin capsules at a mass of 225 mg (45 μg calcitriol). The capsules were then analyzed for stability at 5°C, 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH. At the appropriate time points, the stability samples were analyzed for content of intact calcitriol and dissolution of the capsules. The calcitriol content of the capsules was determined by dissolving three opened capsules in 5 mL of methanol and held at 5°C prior to analysis. The dissolved samples were then analyzed by reversed phase HPLC. A Phenomenex Hypersil BDS C18 column at 30°C was used with a gradient of acetonitrile from 55% acetonitrile in water to 95% acetonitrile at a flow rate of 1.0 mL/min during elution. Peaks were detected at 265 nm and a 25 μL sample was injected for each run. The peak area of the sample was compared to a reference standard to calculate the calcitriol content as reported in Table 5. The dissolution test was performed by placing one capsule in each of six low volume dissolution containers with 50 mL of deionized water containing 0.5% sodium dodecyl sulfate. Samples were taken at 30, 60 and 90 min after mixing at 75 rpm and 37 °C. Calcitriol content of the samples was determined by injection of 100 μL samples onto a Betasil C18 column operated at 1 mL/min with a mobile phase of 50:40:10 acetonitrile:water:tetrahydrofuran at 30°C (peak detection at 265 nm). The mean value from the 90 min dissolution test results of the six capsules was reported (Table 6).

[0135] The chemical stability results indicated that decreasing the MIGLYOL 812 content with a concomitant increase in Vitamin E TPGS content provided enhanced recovery of intact calcitriol as noted in Table 5. Formulation 4 (50:50 MIGLYOL 812/Vitamin E TPGS) was the most chemically stable formulation with only minor decreases in recovery of intact calcitriol after 3 months at 25°C/60% RH, enabling room temperature storage.

TABLE 5: Chemical stability of calcitriol formulation in hard gelatin capsules (225 mg total mass filled per capsule, 45 µg calcitriol)

Storage Condition	Time (mos)	Assay ^a (%)			
		Form. 1	Form. 2	Form 3	Form 4
N/A	0	100.1	98.8	99.1	100.3
5°C	1.0	99.4	98.9	98.9	104.3
25°C/60% RH	0.5	99.4	97.7	97.8	102.3
	1.0	97.1	95.8	97.8	100.3
	3.0	95.2	93.6	96.8	97.9
30°C/65% RH	0.5	98.7	97.7	96.8	100.7
	1.0	95.8	96.3	97.3	100.4
	3.0	94.2	93.6	95.5	93.4
40°C/75% RH	0.5	96.4	96.7	98.2	97.1
	1.0	96.1	98.6	98.5	99.3
	3.0	92.3	92.4	93.0	96.4

a. Assay results indicate % of calcitriol relative to expected value based upon 45 µg content per capsule. Values include pre-calcitriol which is an active isomer of calcitriol.

TABLE 6: Physical Stability of Calcitriol Formulation in Hard Gelatin Capsules (225 mg total mass filled per capsule, 45 µg calcitriol)

Storage Condition	Time (mos)	Dissolution ^a (%)			
		Form. 1	Form. 2	Form 3	Form 4
N/A	0	70.5	93.9	92.1	100.1
5°C	1.0	71.0	92.3	96.0	100.4
25°C/60% RH	0.5	65.0	89.0	90.1	98.3
	1.0	66.1	90.8	94.5	96.2
	3.0	64.3	85.5	90.0	91.4
30°C/65% RH	0.5	62.1	88.8	91.5	97.9
	1.0	65.1	89.4	95.5	98.1
	3.0	57.7	86.4	89.5	88.8
40°C/75% RH	0.5	91.9	90.2	92.9	93.1
	1.0	63.4	93.8	94.5	95.2
	3.0	59.3	83.6	87.4	91.1

a. Dissolution of capsules was performed as described and the % calcitriol is calculated based upon a standard and the expected content of 45 µg calcitriol

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per capsule. The active isomer, pre-calcitriol, is not included in the calculation of % calcitriol dissolved. Values reported are from the 90 min sample.

[0136] The physical stability of the formulations was assessed by the dissolution behavior of the capsules after storage at each stability condition. As with the chemical stability, decreasing the MIGLYOL 812 content and increasing the Vitamin E TPGS content improved the dissolution properties of the formulation (Table 6). Formulation 4 (50:50 MIGLYOL 812/Vitamin E TPGS) had the best dissolution properties with suitable stability for room temperature storage.

EXAMPLE 4

PHASE II CLINICAL TRIAL

[0137] Two hundred fifty patients with androgen independent prostate cancer were enrolled in a randomized placebo controlled trial at 48 centers in the United States and Canada. All patients in the study received chemotherapy treatment with weekly Taxotere[®], a drug in the taxoid class of chemotherapeutic agents. Taxotere[®] is approved for use in prostate cancer and some other types of cancer. Oral dexamethasone was also given along with the Taxotere[®] to minimize certain side effects (allergic reactions and fluid retention) associated with Taxotere[®].

[0138] In addition to Taxotere[®] and dexamethasone, half of the patients were randomly treated with calcitriol and the other half received a placebo. Calcitriol was administered as three capsules of 15 µg each once a week on the day prior to chemotherapy. Previous studies in more than 90 cancer patients suggested that weekly dosing allows patients to receive high doses of calcitriol while minimizing the side effect of high blood calcium (hypercalcemia). The same Taxotere[®] dose of 36 mg/m² body surface area was administered to the patients receiving Taxotere[®] and placebo or Taxotere[®] in combination with calcitriol. Drugs were administered for three weeks out of a four week cycle, with calcitriol being administered on days 1, 7, and 21 and Taxotere[®] being administered on days 2, 8, and 22.

[0139] Patients receiving Taxotere[®] and calcitriol by HDPa experienced fewer GI disorders (as defined in Table 7). The results of the trial are shown in Table 8. One hundred eighteen of the 125 patients on Taxotere[®] and placebo experienced one or more adverse events involving a gastrointestinal disorder as compared to 107 of 125 patients receiving Taxotere[®] and calcitriol ($p < 0.02$). In 19 of 125 patients receiving Taxotere[®] and placebo these events were grade 3 or 4 as compared to 16 of 125 patients receiving Taxotere[®] and calcitriol. Most importantly, 12 of 125 patients in the Taxotere[®] and placebo group has a serious adverse event (requiring hospitalization) as compared to 3 of 125 patients in the Taxotere[®] and calcitriol arm ($p < 0.017$). Hospitalization for dehydration was more common in those patients receiving Taxotere[®] and placebo.

TABLE 7: Gastrointestinal events defined as "GI disorders" for analysis

Abdominal pain	Frequent bowel movements
NOS Abdominal pain lower	Gastrointestinal irritation
Abdominal pain upper	Gastrointestinal motility disorder NOS
Anorexia	Lip ulceration
Appetite decreased NOS	Loose stools
Constipation	Mallory-Weiss syndrome
Dehydration	Mouth ulceration
Diarrhea NOS	Mucosal inflammation NOS
Duodenal ulcer	Nausea
Dyspepsia	Retching
Epigastric discomfort	Stomach discomfort
Eructation	Stomatitis
Faecal abnormality NOS	Tongue ulceration
Faecal incontinence	Vomiting NOS
Flatulence	

TABLE 8: Safety analysis - GI events in all adverse events

Adverse event class	Placebo N = 125	Calcitriol N = 125	P-value
GI event	118 (94.4%)	107 (42.8%)	0.020
Grade 3 or 4 GI event	19 (15.2%)	16 (12.8%)	0.65
SAE GI event	12 (7.6%)	3 (2.4%)	0.017

[0140] Having now fully described the invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

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WHAT IS CLAIMED IS:

1. A method for preventing, treating or ameliorating a gastrointestinal (GI) or bladder disorder in a patient receiving chemotherapy and/or radiation therapy, said method comprising administering to said patient a therapeutically effective amount of active vitamin D compound or a mimic thereof.
2. The method of claim 1, wherein said GI or bladder disorder is induced by or associated with chemotherapy or radiation therapy.
3. The method of claim 1, wherein said disorder is one or more of nausea, vomiting, diarrhea, GI bleeding, esophagitis, stomatitis, xerostomia, mucositis, pancreatitis, colitis, proctitis, fibrosis, constipation, abdominal cramps, abdominal pain, dehydration, malabsorption, anorexia, and weight loss.
4. The method of claim 1, wherein said disorder is one or more of bladder mucositis, cystitis, hemorrhagic cystitis, dysuria, urinary retention, hematuria, and bladder pain.
5. The method of claim 1, wherein said active vitamin D compound or a mimic thereof is administered by high dose pulse administration (HDP), wherein each pulsed dose is a sufficient amount to have a therapeutic effect.
6. The method of claim 1, wherein said active vitamin D compound or a mimic thereof is calcitriol.
7. The method of claim 1, wherein said active vitamin D compound or a mimic thereof is 25-OH vitamin D₃.

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8. The method of claim 1, wherein said active vitamin D compound or a mimic thereof is administered as a unit dosage form comprising about 50% MIGLYOL 812 and about 50% tocopherol PEG-1000 succinate (vitamin E TPGS).

9. The method of claim 8, wherein said unit dosage form further comprises at least one additive selected from the group consisting of an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a suspending agent, a binder, a filler, a plasticizer, a thickening agent, a lubricant, and mixtures thereof.

10. The method of claim 9, wherein one of said additives is an antioxidant.

11. The method of claim 10, wherein said antioxidant is selected from the group consisting of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), or both.

12. The method of claim 11, wherein said unit dosage form comprises BHA and BHT.

13. The method of claim 12, wherein said unit dosage form comprises about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.05% to about 0.35% BHA, and about 0.05% to about 0.35% BHT.

14. The method of claim 13, wherein said unit dosage form comprises about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.35% BHA, and about 0.10% BHT.

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15. The method of claim 8, wherein said unit dosage form is a capsule.

16. The method of claim 15, wherein said capsule is a gelatin capsule.

17. The method of claim 15, wherein the total volume of ingredients in said capsule is 10-1000 μ l.

18. The method of claim 8, wherein said unit dosage form comprises about 10 μ g to about 75 μ g of calcitriol.

19. The method of claim 18, wherein said unit dosage form comprises about 45 μ g of calcitriol.

20. The method of claim 19, wherein said unit dosage form comprises about 45 μ g of calcitriol, about 50% MIGLYOL 812, about 50% vitamin E TPGS, BHA, and BHT.

21. The method of claim 20, wherein said unit dosage form comprises about 45 μ g of calcitriol, about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.35% BHA, and about 0.10% BHT.

22. The method of claim 5, wherein said active vitamin D compound or a mimic thereof is administered no more frequently than once in three days.

23. The method of claim 22, wherein said active vitamin D compound or a mimic thereof is administered no more frequently than once in seven days.

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24. The method of claim 23, wherein said active vitamin D compound or a mimic thereof is administered no more frequently than once in ten days.

25. The method of claim 24, wherein said active vitamin D compound or a mimic thereof is administered no more frequently than once in three weeks.

26. The method of claim 1, wherein said patient is suffering from one or more cancers selected from the group consisting of brain cancer, breast cancer, gastrointestinal cancers comprising colon, colorectal, esophageal, gastric, hepatocellular, pancreatic and rectal cancers, genitourinary cancers comprising bladder, prostate, renal cell and testicular cancers, gynecologic cancers comprising cervical, endometrial, ovarian and uterine cancers, head and neck cancer, leukemias comprising acute lymphoblastic, acute myelogenous, acute promyelocytic, chronic lymphocytic, chronic myelogenous and hairy cell leukemias, non-small-cell and small-cell lung cancers, Hodgkin's and non-Hodgkin's lymphomas, melanoma, multiple myeloma and sarcoma.

27. The method of claim 1, wherein said one or more chemotherapeutic agents are selected from the group consisting of abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, BCG live, bevaceizumab, bexarotene, bleomycin, bortezomib, busulfan, calusterone, camptothecin, capecitabine, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cinacalcet, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone, Elliott's B solution, epirubicin, epoetin alfa, estramustine, etoposide, exemestane, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gemcitabine, gemtuzumab, ozogamicin, gefitinib, goserelin, hydroxyurea, ibritumomab tiuxetan,

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idarubicin, ifosfamide, imatinib, interferon alfa-2a, interferon alfa-2b, irinotecan, letrozole, leucovorin, levamisole, lomustine, meclorethamine, megestrol, melphalan, mercaptopurine, mesna, methotrexate, methoxsalen, methylprednisolone, mitomycin C, mitotane, mitoxantrone, nandrolone, nofetumomab, oblimersen, oprelvekin, oxaliplatin, paclitaxel, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed, pentostatin, pipobroman, plicamycin, polifeprosan, porfimer, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, streptozocin, talc, tamoxifen, tarceva, temozolomide, teniposide, testolactone, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, and zoledronate.

28. The method of claim 1, wherein said radiation treatments are selected from the group consisting of brachytherapy, radionuclide therapy, external-beam radiation therapy, thermotherapy (cryoablation therapy, hyperthermic therapy), radiosurgery, charged-particle radiotherapy, neutron radiotherapy, and photodynamic therapy.

29. The method of claim 1, further comprising administering one or more therapeutic agents used for the prevention, treatment, or amelioration of GI or bladder disorders.

30. The method of claim 29, wherein said one or more therapeutic agents are selected from anti-inflammatory agents, antibiotics, anti-emetic agents, anti-apoptotic agents, anti-anorexic agents, or anti-GI bleeding agents.